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Breast Cancer

Risk, Characteristics, and Prognosis of Breast Cancer after Hodgkin's Lymphoma

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain the differences in risk and aggression of breast cancer for Hodgkin's lymphoma survivors.
2. Describe the difference in breast tumor sites for Hodgkin's lymphoma survivors.
3. Use adapted guidelines for surveillance and treatment of these high-risk patients.

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ABSTRACT

Purpose. **To assess breast cancer (BC) risk after Hodgkin's lymphoma (HL) and compare characteristics, risk of second BC, and prognosis of patients with these BCs with patients with first primary BC.**

Patients and Methods. **We considered all 9,620 women with HL recorded in the Surveillance, Epidemiology and End Results dataset in 1973–2007. We calculated age-period standardized incidence ratios of BC. We compared patient, tumor, and treatment characteristics, risk of second BC, and prognosis between patients with BC after HL ($n = 316$) and patients with other BCs occurring during the same period ($n = 450{,}413$) using logistic regression and Cox models adjusted for confounders.**

Results. **HL patients had a 2.4-fold higher risk for developing BC (95% confidence interval [CI], 2.2–2.7) than the general population. Age at HL diagnosis and radiation therapy influenced this risk. Compared with first primary BCs, BCs after HL were diagnosed at a younger age, at an earlier stage, were less frequently hormone receptor positive, were located more frequently in external quadrants, and were less fre-**

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quently treated using radiotherapy. These patients had a higher risk (adjusted hazard ratio [HR], 2.85; 95% CI, 1.79–4.53) for developing a second BC and had a higher BC mortality risk (adjusted HR, 1.36; 95% CI, 1.05–1.76). The higher mortality risk was only partly explained by the higher occurrence rate of a second BC.

Conclusion. **HL survivors have a higher risk for developing BC, their BCs are more aggressive, they have a higher risk for a second BC occurrence, and they have a poorer prognosis. Guidelines of care should be adapted to decrease the impact of BC in these high-risk patients.** ***The Oncologist*** 2012;17:783–791

Introduction

Hodgkin's lymphoma (HL) is increasing among children and young adults both in Europe and the U.S. [1]. The progress achieved in intensive radiotherapy over the past decades has made HL become a curable disease in ~75% of patients [2]. Although these results are reflecting a therapeutic success, the same treatment has increased the risk for second radiotherapy-induced malignancies [3–6]. Breast cancer (BC) is the most common second malignancy after radiotherapy for HL in women [7].

Numerous studies have evaluated the higher BC risk after HL than in the general population [8–15]. Some studies have assessed if BC following HL differs from primary BC in terms of tumor characteristics [16–19] or prognosis [8, 17–22]. In particular, a large population-based study using the dataset from the Surveillance, Epidemiology and End Results (SEER) program reported that, among women with localized BC, patients with previous HL had a twofold greater risk for death resulting from BC than patients without previous HL [18]. Also, a large hospital-based study reported that HL survivors had a higher risk for metachronous contralateral BC [19].

To date, no single population-based study has reported, at the same time, the determinants of BC risk after HL; differences from other BCs concerning patient, tumor, and treatment characteristics; second BC cancer occurrence; or prognosis accounting for putative confounders. In particular, no study has evaluated if the poorer prognosis for BC after HL is linked to different tumor profiles or to the higher risk for developing a second BC. This study aimed to answer these questions in order to help clinicians in this delicate area of BC occurring among HL survivors.

Patients and Methods

Risk for a Second BC after HL

We used data from the SEER program of the National Cancer Institute [23]. We included all 9,620 women with first primary HL diagnosed in 1973–2007. We considered all 316 BCs occurring ≥6 months after HL until 2007. The variables examined were age at diagnosis of HL, period of diagnosis, latency (interval between HL and BC), and radiotherapy. The SEER program does not collect specific information on chemotherapy regimens. We did not consider HL stage at diagnosis because of changes in codification during the study period.

Characteristics and Outcome of BCs Occurring after HL and First Primary BCs

We included all BCs after HL ($n = 316$) and all 450,413 other first primary BCs that occurred in July 1, 1973 to December 31, 2007. Variables of interest were age at diagnosis of BC, period of BC diagnosis, stage, grade, hormone receptor status (available only since 1990), type of surgery, radiotherapy, second BC occurrence, survival, and cause of death.

Statistical Analysis

Risk for BC after HL

We calculated person-years at risk for developing BC starting from 6 months after the date of HL to the date of BC diagnosis, date of death, or December 31, 2007, whichever came first. The expected number of BCs was calculated by multiplying the period- and age-specific cancer incidence rates of the SEER population by the person-years. The standardized incidence ratio (SIR) was calculated as the ratio between the observed and expected numbers of cases. A two-tailed 95% confidence interval (CI) of the SIR was calculated assuming a Poisson distribution of the observed numbers. We calculated the excess absolute risk (EAR) of BC per 10,000 as the difference between the observed and expected numbers of cases divided by the person-years at risk multiplied by 10,000. Analyses were conducted using the SEER statistics software. We calculated the cumulative risk for BC occurrence across time using the Kaplan–Meier method.

Characteristics and Outcome of BC Occurring after HL and First Primary BC

We compared patient, tumor, and treatment characteristics using logistic regression analysis considering women with BC occurring after HL as cases and all other first primary BC cases as controls. With univariate logistic regression analysis, we identified which covariates were significantly associated with cases. Then, to identify characteristics independently associated with cases, we performed a multivariate logistic regression, entering in the model all variables that were significant in the univariate analysis.

We evaluated second BC occurrence after exclusion of women treated using bilateral mastectomy for the first BC and women with bilateral BC. We considered all BCs occurring after 1 month following the first BC as second BCs. We compared the risk for a second BC between BC patients with and without previous HL using a Cox model, accounting for other variables significantly linked to this event occurrence. We also calculated the cumulative risk for a second BC at 5 years.

We evaluated BC prognosis considering both the BC-specific survival time, defined as the interval between the date of diagnosis and the date of death from BC, and the overall survival time, defined as the interval between the date of diagnosis

and the date of death from any cause. We used multivariate analysis using a Cox regression model to evaluate the impact on prognosis of having HL before BC after adjusting for other prognostic factors. In a second step, we evaluated if the difference in the BC-specific survival time between BC patients with and without previous HL was a result of a difference in second BC occurrence by excluding patients with a second BC from the analysis.

All tests were two-sided. Statistical significance was established at $p < .05$. Analyses were conducted using SPSS (version 15.0.1; SPSS, Inc., Chicago, IL).

Results

The characteristics of the 9,620 women with HL are presented in Table 1. The mean age of patients at HL diagnosis was 47.9 years (range, 2–96 years). The median follow-up time for the whole cohort was 9.83 years (range, 0.5–34.9 years) and the total person-years at risk for developing BC was 104,064. Overall, 316 patients with HL developed BC, with an overall SIR of 2.4 (95% CI, 2.2–2.7). The risk (SIR) for a subsequent BC was highest among patients aged ≤19 years at HL diagnosis (SIR, 13.4; 95% CI, 10.5–17.0) and decreased progressively with advancing age at HL diagnosis to approach the expected rate in the general population when HL was diagnosed at age ≥50 years (SIR, 1.0; 95% CI, 0.8–1.4). The BC risk was higher for HL patients diagnosed in the earlier periods and was observed in all ethnic groups (data not shown). The higher risk for BC emerged 5 years after HL onward. The risk for BC was higher for HL patients who received radiotherapy (SIR, 3.2; 95% CI, 2.8–3.6) than for HL patients who did not (SIR, 1.4; 95% CI, 1.1–1.7). Overall, 18 additional BCs were observed for 10,000 person-years with HL (EAR). Figure 1 shows the cumulative risk for BC occurrence according to the use of radiotherapy among the female HL cohort. The difference in risk between the radiotherapy and no radiotherapy groups appeared clearly after 15 years and persisted for at least 30 years after.

Table 2 shows the characteristics of BC patients diagnosed after HL versus first primary BC patients. BC patients with previous HL were younger: 32% were aged <40 years, compared with 7% among the other BC patients. BC after HL was more often diagnosed in the most recent study period. After HL, BC more often occurred in the external quadrants (adjusted odds ratio [OR] for internal versus external location, 0.61; 95% CI, 0.42–0.89 among BC patients with previous HL compared with other BC patients). Women with previous HL had a lower risk for advanced BC at diagnosis (adjusted OR for advanced versus localized stage, 0.63; 95% CI, 0.49–0.82), whereas tumors of women who had HL less likely expressed estrogen receptor (ER) and progesterone receptor (PR) (adjusted OR for ER^- and PR^- versus ER^+ or PR^+, 1.34; 95% CI, 0.99–1.81). As expected, BC patients who had been treated for HL less frequently received breast-conserving surgery than other patients (adjusted OR for breast-conserving surgery versus mastectomy, 0.51; 95% CI, 0.37–0.69) and less frequently received radiotherapy (adjusted OR for radiotherapy, yes versus no, 0.30; 95% CI, 0.22–0.42).

Stratification of the HL cohort by treatment group showed that the higher incidence of external quadrant tumors was limited to women who had radiotherapy for HL (Table 3). Similarly, the lower use of breast-conserving surgery and radiotherapy was observed only for women who had previous radiotherapy for HL (Table 3).

BC patients with previous HL more frequently developed a second BC. In a logistic regression, the adjusted OR for a second BC versus no second BC was 2.50 (95% CI, 1.63–3.83) for BC patients with previous HL compared with other BC patients (Table 2). In a Cox model accounting for other variables significantly linked to a second cancer occurrence (i.e., age and period at first BC diagnosis, ethnicity, breast quadrant, stage, differentiation, ER status, type of surgery, radiotherapy), the risk (hazard ratio [HR]) for a second BC for BC patients with versus without previous HL was 2.85 (95% CI, 1.79–4.53; $p < .0000$). Also, the delay in second BC occurrence was shorter for BC patients with previous HL than for other BC patients (mean delay, 4.1 years versus 7.8 years; p-value for Fisher test = .001). The 5-year cumulative risk was 5.75% (95% CI, 2.64%–8.7%) in HL patients, compared with 2.24% (95% CI, 2.19%–2.30%) in non-HL patients.

In a crude analysis, the BC-specific survival rates were similar among patients with BC following HL (74.6%; 95% CI, 68.2%–81.0%) and other BC patients (75.1%; 95% CI, 75.0%–75.2%) (p-value for log-rank test = .961). Table 4 shows comparisons using adjusted Cox models of BC prognosis between patients with previous HL and those without a history of HL. A history of HL led to worse BC-specific survival and overall survival times: the multiadjusted (for patients and treatment characteristics) HR was 1.36 (95% CI, 1.05–1.76) for BC-specific mortality and 2.21 (95% CI, 1.85–2.67) for overall mortality. The higher mortality rate also persisted when adjusting for hormone receptor status considering only the period 1990–2007, when data were available (HR for BC-specific mortality, 1.59; 95% CI, 1.20–2.10).

After exclusion of all BC patients who developed a second BC, the higher mortality risk linked to BC in the HL group was slightly lower, 1.25 versus 1.36 (multiadjusted HR), and was no longer significant (95% CI, 0.94–1.66).

Discussion

This study confirms a higher risk for BC after HL, which is particularly important when HL occurs at a young age and when HL is treated using radiotherapy, and this risk persists over 30 years after HL diagnosis. Women with HL after the age of 50 did not have a higher risk for a second BC. This study also confirms that patients with BC after HL more frequently have hormone receptor–negative tumors and less frequently receive radiotherapy. We show, for the first time, that the higher incidence of BC occurs in external breast quadrants. We also confirm the important risk for developing a second BC among HL survivors with BC. These women also present a poorer BC prognosis, which is not explained by differences in patient, tumor, or treatment characteristics and is only partly linked to the higher rate of a second BC occurrence.

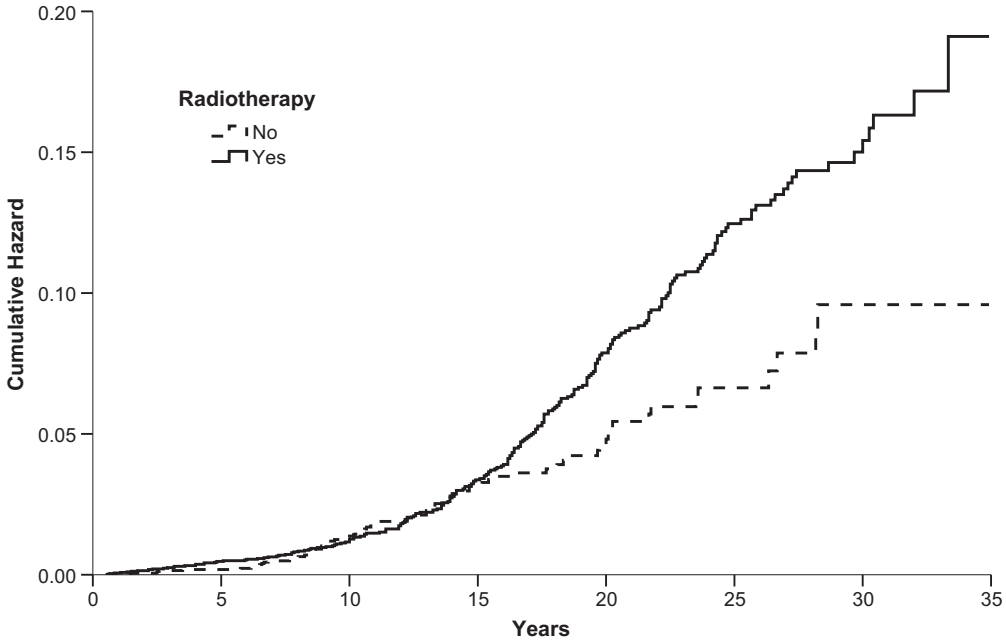
Table 1. Risk for breast cancer among female patients with HL according to patient and treatment

Characteristic	*n* of HL patients	Observed *n* of breast cancers	Expected *n* of breast cancers	SIR: observed/expected	(95% CI)
Age at HL diagnosis, yrs					
≤19	1,526	69	5.1	13.4[b]	(10.5–17.0)
20–29	3,062	108	24.8	4.4[b]	(3.6–5.3)
30–39	1,988	61	31.3	2.0[b]	(1.5–2.5)
40–49	950	29	20.9	1.4	(0.9–2.0)
≥50	2,094	49	47.4	1.03	(0.8–1.4)
Period of HL diagnosis					
1973–1979	1,569	108	33.6	3.2[b]	(2.6–3.9)
1980–1989	2,692	150	50.4	3.0[b]	(2.5–3.5)
1990–2007	5,359	58	45.5	1.3	(1.0–1.6)
Latency, yrs					
<2	9,620	9	13.0	0.7	(0.3–1.3)
<5	8,220	19	21.6	0.9	(0.5–1.4)
<10	6,600	45	29.9	1.5[a]	(1.1–2.0)
<15	4,633	78	24.6	3.2[b]	(2.5–4.0)
<20	3,081	87	19.2	4.5[b]	(3.6–5.6)
≥20	1,776	78	21.1	3.7[b]	(2.9–4.6)
Radiotherapy for HL					
Yes	5,176	234	73.3	3.2[b]	(2.8–3.6)
No	4,193	74	53.2	1.4[a]	(1.1–1.8)
Unknown	251	8	3.0	2.7[a]	(1.2–5.1)
Total	9,620	316	129.5	2.4[b]	(2.2–2.7)

The SIR was calculated as the ratio between the observed and expected numbers of cases. The expected number of breast cancers for each category was calculated by multiplying the period- and age-specific cancer incidence rates of the Surveillance, Epidemiology, and End Results population by the person-years at risk for the category.
[a]$p < .01$.
[b]$p < .001$.
Abbreviations: CI, confidence interval; HL, Hodgkin's lymphoma; SIR, standardized incidence ratio.

Our study is the first to report that BC after HL occurs more frequently in external breast quadrants. Three older studies reported a high incidence of tumors in the inner quadrants [7, 16, 24]. This discrepancy could probably be explained by a change in radiation patterns, including dose, equipment, and radioprotection. In the early 1970s, radiotherapy was based on research by Kaplan and Rosenberg, enhancing large fields of irradiation, in particular, including the mediastinum [25–27]. Since the 1980s, these fields have been limited with progressive changes in radiation equipment from telecobalt to linear accelerators, which required a higher dose to superficial structures of the thorax [28]. Our observation of a higher risk in external quadrants can be explained by these changes, in particular, by the mantle field irradiation and the exposure of supradiaphragmatic structures. The external quadrants are located outside the shielded lung protection area and therefore receive the full dose of ionizing radiation [29] (Fig. 2). This study confirms that HL patients have a higher risk for developing BC, with an overall risk that is 2.4 times higher than in the general population and an EAR of 18 additional BC per 10,000 person-years. Close estimates have been reported in other studies [5, 7, 30, 31]. Our results also confirm other findings available in the literature, such as a particularly important risk for BC when HL occurs at young age, with a decreasing risk with increasing age [4, 8, 10, 12, 30, 32]. A new finding of this study is the absence of a higher risk for a second BC when HL occurs after the age of 50 years. This finding supports the hypothesis that the hormonal environment is also required for the development of BC.

Our findings are consistent with many retrospective studies showing a higher risk for BC when HL is treated with radiotherapy [12, 24]. Additionally, we observed the same BC risk among patients with previous HL, independently from radiotherapy, up until 15 years after HL diagnosis, and then the risk increased in the irradiated group (Fig. 1). The higher BC risk persisted >30 years after diagnosis of HL. We also found that patients with BC after HL less frequently underwent breast-conserving surgery (which, according to international guide-



Radiotherapy	0 - 4 yrs		5 - 9 yrs		10 - 14 yrs		15 - 19 yrs		20 - 24 yrs		25 - 29 yrs		30 - 34 yrs	
	n	Obs	*n*	Obs	*n*	Obs	*n*	Obs	*n*	Obs	*n*	Obs	*n*	Obs
No	4,196	6	2,558	22	1,645	24	975	10	497	8	225	4	67	0
Yes	5,172	21	3,922	23	2,928	54	2,100	75	1,306	44	673	12	242	5

Figure 1. Cumulative risk for subsequent breast cancer occurrence among the cohort of female patients with Hodgkin's lymphoma according to the use of radiotherapy.

Curves were calculated using the Kaplan–Meier method; *p*-value for log rank test $<.000$.

n is the number of persons at risk at the beginning of the period of follow-up. *Obs* is the number of observed cases of breast cancer during the period of follow-up.

lines, necessarily would include radiotherapy) and/or radiotherapy because of previous radiotherapy for HL [19].

Our study also confirms that BC after HL occurs at a younger age than other BCs [8, 19, 30, 31]. This is because of the known sensitivity to ionizing radiation of breast tissue in younger aged patients [33, 34]. In this population, 32% of patients with BC following HL were aged <40 years, compared with 7% of BC patients without a history of HL.

We found that women with previous HL were more likely to have BC diagnosed at a localized stage than other BC patients, probably because of better surveillance of these women [19, 20, 35]. However, an earlier stage at diagnosis was not reported in previous studies [14, 20], and this probably depends on the period considered, screening generalization and recommendations, in particular, concerning the age to start screening.

Our results show that women with BC after HL more frequently have tumors with a negative hormone receptor status. This was not linked to an age difference because comparisons were made using a multiadjusted logistic regression that included age. Our study confirms the previous results of one large population-based study [14], but contrasts with other small hospital-based case–control studies [36, 37] and with a large multicentric study [19]. Although hormonal stimulation appears to play a role in the development of radiotherapy-induced BC [13, 38], the etiology and natural history probably differ between hormone receptor-negative and hormone receptor-positive tumors [39]. The effect of radiotherapy directly on breast tissue or indirectly via castration of ovarian function could preferably trigger the occurrence of hormone receptor-negative tumors [40]. As a counterpart, we did not observe significant differences in terms of tumor grade, as previously observed in other studies [14, 17, 32, 36, 37, 41]. The slight differences we observed in grade in the crude comparison disappeared after adjustment for other factors, including hormone receptor status and age.

Our study confirms that women with BC occurring after HL have a higher risk for developing a second BC. Elkin et al. [19] recently reported that women with BC among HL survivors have a nearly fourfold greater risk for developing a second metachronous BC, with a cumulative risk of 18% at 5 years, similar to the characteristics of *BRCA1* and *BRCA2* mutation carriers [42, 43]. In our study, accounting for confounders, the risk for a second BC was nearly threefold greater, with a cumulative rate at 5 years of 6%, lower than that reported previously [19]. This may be a result of differences in the study

Table 2. Characteristics of BCs occurring after HL versus other BCs

Characteristic	BCs after HL, $n = 316$ (100%) (cases)	Other BCs, $n = 450{,}413$ (100%) (controls)	p-value for heterogeneity	Adjusted odds ratio[a]	(95% CI)
Age at diagnosis of BC, yrs			<.000		
<40	100 (31.6)	30,163 (6.7)		1	
40–59	161 (50.9)	181,052 (40.2)		0.25[g]	(0.20–0.33)
≥60	55 (17.4)	239,198 (53.1)		0.06[g]	(0.04–0.09)
Period of diagnosis of BC			<.000		
1973–1984	14 (4.4)	108,415 (24.1)		1	
1985–1996	92 (29.1)	161,921 (35.9)		1.89	(0.92–3.89)
1997–2007	210 (66.5)	180,077 (40.0)		5.28[g]	(2.54–10.95)
Breast quadrant			.010		
External	153 (48.4)	180,311 (40.0)		1	
Internal	32 (10.1)	60,497 (13.4)		0.61[g]	(0.42–0.89)
Other	81 (25.6)	117,582 (26.1)		0.78	(0.59–1.02)
Unknown	50 (15.8)	92,023 (20.4)		0.65[e]	(0.47–0.91)
Second breast cancer occurrence[b]			.002		
No	262 (87.9)	414,212 (92.9)		1	
Yes	24 (8.1)	18,852 (4.2)		2.50[f]	(1.63–3.83)
Unknown[c]	12 (4.0)	12,788 (2.9)		1.03	(0.57–1.84)
Stage			.043		
Localized	203 (64.2)	259,149 (57.5)		1	
Regional	89 (28.2)	147,100 (32.7)		0.63[f]	(0.49–0.82)
Distal	19 (6.0)	27,665 (6.1)		1.00	(0.59–1.62)
Unknown	5 (1.6)	16,499 (3.7)		0.73	(0.28–1.91)
Differentiation					
Well	31 (9.8)	47,795 (10.6)	<.000	1	
Moderate	89 (28.2)	110,808 (24.6)		1.10	(0.73–1.66)
Poor	126 (39.9)	114,803 (25.5)		1.24	(0.83–1.86)
Unknown	70 (22.2)	177,007 (39.3)		1.14	(0.72–1.81)
Steroid hormone receptors[d]					
ER^+ or PR^+	156 (55.7)	182,111 (65.2)	<.000	1	
ER^- and PR^-	75 (26.8)	46,277 (16.6)		1.34	(0.99–1.81)
Unknown	49 (17.5)	50,827 (18.2)		1.15	(0.82–1.62)
Type of surgery			<.000		
Mastectomy	224 (70.9)	180,438 (40.1)		1.00	
Breast conserving	72 (22.8)	157,400 (34.9)		0.51[g]	(0.37–0.69)
Other	6 (1.9)	80,637 (17.9)		0.17[f]	(0.06–0.49)
None	13 (4.1)	17,882 (4.0)		0.61	(0.32–1.15)
Unknown	1 (0.3)	14,056 (3.1)		0.22	(0.03–1.74)
Radiotherapy			<.000		
No	252 (79.9)	269,945 (59.9)		1	
Yes	55 (17.4)	168,436 (37.4)		0.30[g]	(0.22–0.42)
Unknown	9 (2.8)	12,032 (2.7)		0.80	(0.41–1.58)

Odds ratios are derived from logistic regression considering patients with previous Hodgkin's lymphoma as cases and other patients as controls.
[a]Adjusted for all variables significant in the univariate analysis, that is, age at BC, period at BC diagnosis, ethnicity, localization, stage, differentiation, surgery and radiotherapy.
[b]Second breast cancer occurring ≥1 month after the first BC.
[c]Patients lost to follow-up.
[d]Analysis restricted to the 1990–2007 period ($n = 279{,}495$).
[e]$p < .05$.
[f]$p < .01$.
[g]$p < .001$.
Abbreviations: BC, breast cancer; CI, confidence interval, ER, estrogen receptor; HL, Hodgkin's lymphoma; PR, progesterone receptor.

Table 3. Comparison of BCs occurring after HL (cases) versus other BCs (controls) according to the use of radiotherapy for the lymphoma

	Cases without radiotherapy for HL ($n = 74$) versus controls		Cases with radiotherapy for HL ($n = 234$) versus controls	
Characteristic	**Adjusted odds ratio[a]**	**(95% CI)**	**Adjusted odds ratio[a]**	**(95% CI)**
Breast quadrant				
External	1		1	
Internal	1.03	(0.50–2.12)	0.53[c]	(0.33–0.83)
Other	1.28	(0.73–2.22)	0.63[b]	(0.45–0.87)
Unknown	1.05	(0.53–2.09)	0.59	(0.41–0.87)
Type of surgery				
Mastectomy	1		1	
Breast conserving	0.75	(0.45–1.24)	0.19[d]	(0.13–0.27)
Other	–		0.37	(0.11–1.30)
None	1.21	(0.40–3.68)	0.51	(0.23–1.12)
Unknown	–		0.36	(0.05–2.89)

Odds ratios are derived from logistic regression considering patients with previous HL as cases and other patients as controls.
[a]Adjusted for all variables significant in the univariate analysis, that is, age at BC, period at BC diagnosis, ethnicity, localization, stage, differentiation, surgery, and radiotherapy.
[b]$p < .05$.
[c]$p < .01$.
[d]$p < .001$.
Abbreviations: BC, breast cancer; CI, confidence interval; HL, Hodgkin's lymphoma.

Table 4. Comparison of prognosis between BCs occurring after HL and other BCs

Outcome	**HR adjusted for age at BC (continuous)**	**(95% CI)**	**HR also adjusted for patient and tumor characteristics (1)**	**(95% CI)**	**HR also adjusted for treatments (2)**	**(95% CI)**
BC-specific mortality						
Previous HL						
No	1		1		1	
Yes	1.08	(0.83–1.39)	1.41[a]	(1.08–1.82)	1.36[a]	(1.05–1.76)
Overall mortality						
Previous HL						
No	1		1		1	
Yes	1.86[b]	(1.55–2.23)	2.28[b]	(1.89–2.74)	2.21[b]	(1.85–2.67)

HR derived from Cox model (1) adjusted for age at BC, period at BC diagnosis, ethnicity, localization, and stage (2) idem plus surgery and radiotherapy.
[a]$p < .05$.
[b]$p < .001$.
Abbreviations: BC, breast cancer; CI, confidence interval; HL, Hodgkin's lymphoma; HR, hazard ratio.

design (hospital-based matched cohort study) and the lower number of cases. Our study also shows that a second BC after HL occurs earlier than other second BCs.

We report a poorer prognosis for BC patients when occurring after HL, compared with a first primary BC, after adjustment for differences in patient characteristics, tumor profile, and treatment. Only two previous studies have also adjusted BC mortality risk after HL on putative confounders, and these reported similar results. Milano et al. [18] showed 40% higher BC incidence, and Elkin et al. [19] showed a 60% higher BC mortality, which was, however, not significant. As in our study, no difference in risk was observed when only crude specific mortality or survival was considered [16, 20, 44]. We also evaluated if the greater BC mortality among HL survivors who developed BC was linked to their higher risk for developing a second BC than in other BC patients. When we excluded all

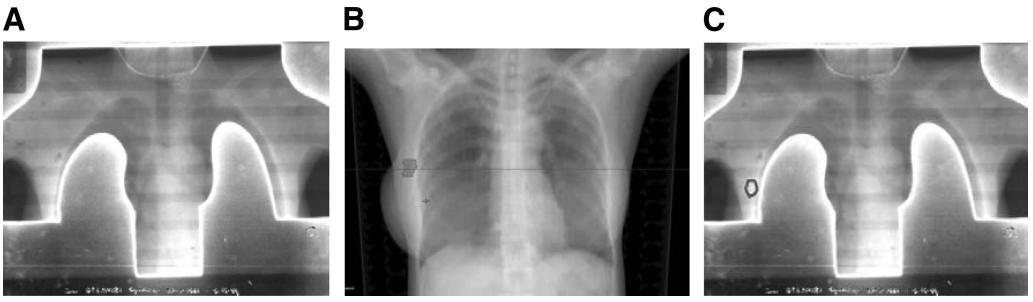


Figure 2. Breast cancer development in a patient after radiotherapy for Hodgkin's lymphoma. **(A):** Irradiation field of a Geneva University Hospitals patient treated for stage IIA Hodgkin's lymphoma in 1994. **(B):** Breast cancer diagnosis in the same patient in 2001, **(C):** Superimposition of **(A)** and **(B)**.

BC patients who had a second BC, the higher mortality among HL survivors with BC was lower at 25%, versus 36%. Therefore, the higher risk for a second BC occurrence only partially explains the higher BC mortality observed.

Limitations of this study are the lack of information on chemotherapy and on dose and type of radiation in the SEER dataset. In particular, differences in the use of chemotherapy between BC patients with and without previous HL could be one of the reasons for the poorer prognosis if patients with HL received fewer prescriptions. Also, we do not have data on how radiotherapy was delivered. The only hints come from published research along our study's timeline. We cannot evaluate the effect of different radiotherapy protocols on the risk for a second BC.

The strengths of this study are that it is population-based with high power and analytical approaches that permit accounting for important confounders when comparing BC characteristics and mortality.

This study provides a broad overview on BC after HL, including both the presentation and prognosis. The clinical implications comprise extra protection of breast tissue during treatment for HL, greater screening surveillance of the breast (as recommended for *BRCA1* and *BRCA2* mutation carriers), discussion about the opportunity for HL survivors with BC to be offered closer surveillance and prophylaxis of the contralateral breast to prevent or detect early a second BC occurrence, and, finally, to provide more aggressive treatment because of the poorer prognosis of BC patients after HL.

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